

Do larger cholesterol reductions produce larger, and worthwhile, coronary heart disease reductions in high-risk individuals?

There is general agreement that cholesterol is an important cause of coronary heart disease (CHD), perhaps even for those with average or below-average cholesterol. In observational studies, the continuous relationship between CHD risk, when plotted on a doubling scale, and blood cholesterol level is roughly linear. So, for example, a prolonged difference of about 1 mmol/l in blood cholesterol is associated with about 50% less CHD, irrespective of the baseline cholesterol level. Similarly, a prolonged difference of 2 mmol/l corresponds to about 75% less CHD.

In the Scandinavian Simvastatin Survival Study (4S), an average 1.7 mmol/l reduction in blood total cholesterol with simvastatin was associated with a highly significant reduction of about one-third in myocardial infarction (MI) and other major coronary events. But, although 4S and other more recent studies have demonstrated worthwhile benefits with HMG CoA reductase inhibitor ("statin") therapy in some types of very high-risk patients, such patients are still at elevated risk of CHD with the statin regimens studied. For example, about one-fifth of the post-MI patients allocated 20-40 mg daily simvastatin in 4S still had major CHD events during 5 years of follow-up. Observational epidemiological studies indicate that a lower risk of CHD is associated with a lower blood cholesterol level, down at least to 3 mmol/l. But, direct randomised evidence of the effects on CHD of a larger cholesterol reduction than that produced by standard-dose statin regimens is lacking.

SEARCH aims to demonstrate reliably whether a more intensive cholesterol-lowering regimen of 80 mg daily simvastatin produces larger, and worthwhile, reductions in CHD than does a standard 20 mg daily regimen. An average difference in blood cholesterol of about 0.5 mmol/l might produce at least a 15-20% further reduction in CHD. In order to be able to detect such an effect on CHD reliably, about 12,000 MI survivors in whom statin therapy is considered to be clearly indicated are to be studied for about 5 years.

Does reducing homocysteine levels with folic acid and vitamin B₁₂ reduce vascular disease risk?

There is consistent evidence from a large number of epidemiological studies of a positive association between blood levels of total homocysteine and the risk of occlusive vascular disease. Taken together, the epidemiological evidence indicates that, throughout the range studied, a prolonged 3-4 $\mu\text{mol/l}$ lower blood homocysteine level might be associated with about one-third less vascular disease. But there is, as yet, very little randomised controlled evidence about the effects on vascular disease of lowering blood homocysteine levels.

If, as for cholesterol lowering, much of the lower risk of occlusive vascular disease associated epidemiologically with lower blood homocysteine levels appears within just a few years then an average reduction of about 3-4 $\mu\text{mol/l}$ might produce at least a 15-20% reduction in CHD. Such reductions in blood homocysteine can be achieved by increasing consumption of folic acid and vitamin B₁₂. Hence, patients in SEARCH will also be randomly allocated to receive a daily dose of 2 mg folic acid plus 1 mg vitamin B₁₂, or matching placebo, for about 5 years in a 2 x 2 factorial study. Such a study design allows **all** randomised patients to contribute **fully** to assessment of the separate effects of additional reductions in blood cholesterol and in blood homocysteine.

SEARCH: a streamlined trial collecting only essential data

The reliable assessment of the important questions that SEARCH is addressing requires the randomisation of a very large number of high-risk patients, and their treatment and follow-up for several years. To be able to study about 12,000 post-MI patients for about 5 years, SEARCH is streamlined: extra work for collaborating doctors and hospitals has been kept to a minimum, only essential data are being collected, and special clinic staff are employed to carry out all the study procedures.

SUMMARY OF THE STUDY AIMS AND DESIGN

**Front
cover**

1. BACKGROUND AND RATIONALE

1.1 RELIABLE ASSESSMENT OF THE EFFECTS OF PRODUCING GREATER BLOOD CHOLESTEROL REDUCTIONS THAN WITH STANDARD "STATIN" REGIMENS 3

Observational epidemiological studies indicate that lower blood cholesterol levels are associated with lower CHD risk throughout the "normal" UK range
 Observational relationship between blood cholesterol levels and CHD risk: 1 mmol/l PROLONGED difference in blood cholesterol corresponds to about 50% less CHD
 Modest effects on CHD in randomised trials of treatments that lowered blood cholesterol by only about 10%
 Experience with HMG CoA reductase inhibitors ("statins"): greater blood cholesterol reductions appear to produce greater CHD reductions
 Experience with higher-dose statin regimens
 SEARCH: to determine whether larger blood cholesterol reductions produce larger, and worthwhile, CHD reductions in high-risk individuals

1.2 RELIABLE ASSESSMENT OF THE EFFECTS OF REDUCING BLOOD HOMOCYSTEINE LEVELS BY FOLIC ACID PLUS VITAMIN B₁₂ THERAPY 7

Homocysteine metabolism and risk of occlusive vascular disease
 Epidemiological associations between elevated blood homocysteine levels and occlusive vascular disease
 Evidence for a causal link between blood homocysteine levels and occlusive vascular disease
 Reducing blood homocysteine levels by folic acid plus vitamin B₁₂ therapy
 SEARCH: an opportunity to obtain substantial randomised controlled evidence about the effects of homocysteine-lowering therapy on vascular disease

2. SEARCH: PLAN OF INVESTIGATION

2.1 AIMS 11

2.2 TREATMENT COMPARISONS 11

Run-in period prior to randomisation
 Random allocation of higher-dose versus standard-dose simvastatin, and folic acid plus vitamin B₁₂ versus placebo
 Full efficiency of 2 x 2 factorial design: separate assessment of both study questions without any material effect on non-drug cost or sample size requirements

2.3 ASSESSMENT OF OUTCOME 13

Primary assessments
 Secondary assessments
 Tertiary assessments

2.4 SAMPLE SIZE AND PREDICTED NUMBER OF EVENTS 14

At least 1900 CHD events among 12,000 individuals at very high risk of CHD

2.5 DATA AND SAFETY MONITORING	15
Interim analyses: role of the Data Monitoring Committee and Steering Committee Monitoring of any serious adverse experiences believed to be due to study treatment	
2.6 CENTRAL COORDINATION AND COLLABORATING CLINICS	16
Central coordination by the Clinical Trial Service Unit Organisation of study clinics in collaborating hospitals Source of support and non-negligent liability cover Publication in the names of all collaborators	
3. SUMMARY OF PRACTICAL PROCEDURES (see Hospital Manual for details)	
FLOWCHART	19
3.1 ELIGIBILITY AND IDENTIFICATION OF SUITABLE PATIENTS	20
Eligibility for the study Identification of potentially eligible patients and invitation to Screening clinics	
3.2 SCREENING CLINIC VISIT (-2 MONTHS)	21
Relevant medical history and eligibility recorded Invitation to participate in the randomised study and patient consent sought Blood sample taken and pre-randomisation Run-in treatment provided	
3.3 RANDOMISATION CLINIC VISIT (0 MONTHS)	22
Final check of eligibility and compliance before randomisation Random allocation of study treatment	
3.4 POST-RANDOMISATION FOLLOW-UP (2, 4, 8 & 12 months, THEN 6-monthly)	23
Recording adverse events and compliance Blood sample taken and study treatment provided Telephone Follow-up for randomised patients not attending Clinic Follow-up	
3.5 EARLY RECALL CLINIC VISITS AND MODIFYING STUDY TREATMENT	24
Monitoring significant biochemical abnormalities or other problems Modifying study treatment	
3.6 REPORTING SERIOUS ADVERSE EXPERIENCES	25
Immediate reporting of any serious adverse experiences believed to be due to study treatment Reporting of other serious adverse experiences at routine follow-up	
3.7 CENTRAL ASCERTAINMENT OF BIOCHEMICAL EFFECTS, AND OF VASCULAR EVENTS, CANCERS AND CAUSE-SPECIFIC MORTALITY	25
Assessing biochemical efficacy of treatments in a random sample of patients Confirmation of non-fatal events by the coordinating centre Follow-up of deaths and of non-fatal cancers Independent checking of central coding	
APPENDIX 1: Information Leaflet for potentially eligible patients	27
APPENDIX 2: Consent Form	30
REFERENCES	31
STEERING AND DATA MONITORING COMMITTEES, AND CONTACT DETAILS FOR COORDINATING CENTRE	Back cover

1. BACKGROUND AND RATIONALE

1.1 RELIABLE ASSESSMENT OF THE EFFECTS OF PRODUCING GREATER BLOOD CHOLESTEROL REDUCTIONS THAN WITH STANDARD "STATIN" REGIMENS

Observational epidemiological studies indicate that lower blood cholesterol levels are associated with lower CHD risk throughout the "normal" UK range

There is general agreement that, for people in Europe or America with above-average blood cholesterol values, cholesterol is an important cause of coronary heart disease (CHD), and there is now evidence that cholesterol may also be an important cause of CHD even for those with **average** or **below-average** cholesterol levels¹⁻⁴. For, if the population is divided into five equal-sized groups on the basis of their "usual" cholesterol level, there is a steady progression of CHD mortality rates between one group and the next (Figure 1). Even in the lowest of these five groups both the mean cholesterol level and the mean CHD death rate are still substantially higher than in many parts of Asia.

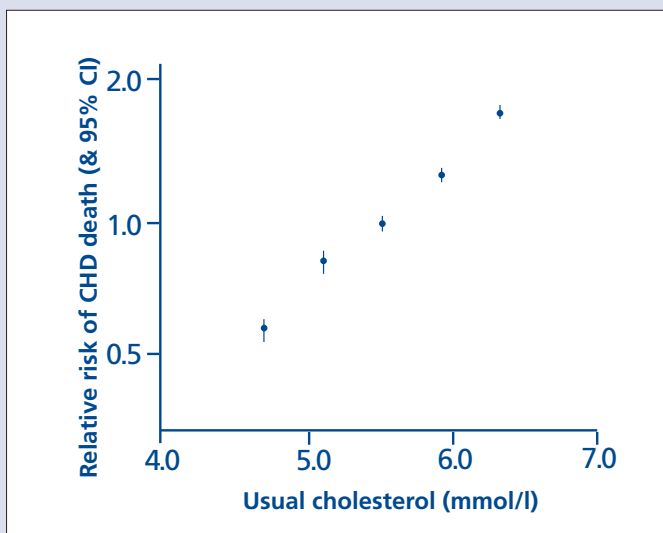


Figure 1: No "threshold" WITHIN Western blood cholesterol normal range: MRFIT prospective follow-up study of 360,000 middle-aged US males, subdivided with respect to usual blood cholesterol and followed for an average of 16 years^{1,2}. (N.B. Usual cholesterol has been derived from baseline cholesterol by correcting for "regression dilution"⁶.)

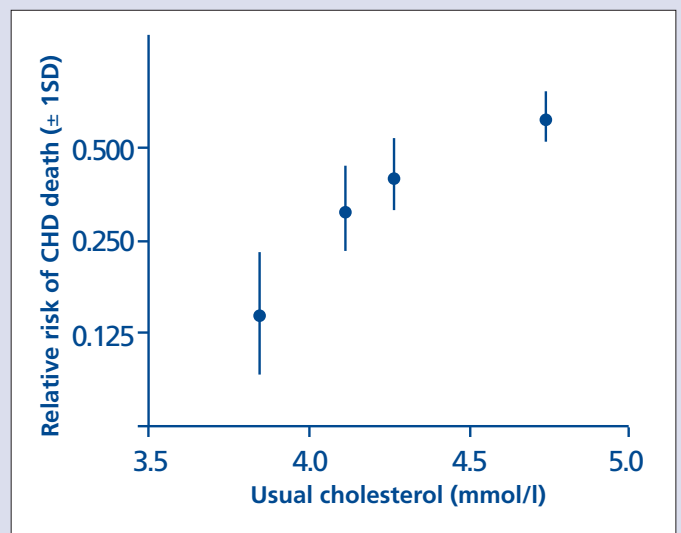


Figure 2: No "threshold" BELOW Western blood cholesterol normal range: Shanghai prospective study in a low cholesterol population of 9000 urban Chinese followed for 8-13 years⁶.

Widespread surveys in rural China have revealed mean cholesterol levels of about 3 mmol/l, with some communities having mean levels as low as 2 mmol/l, and mean CHD death certification rates in middle age of only about 5% of those in Britain⁵. Prospective studies in Asian populations show that the positive relationship between CHD risk and blood cholesterol continues down at least to 3 mmol/l (i.e. well below the range commonly seen in Western populations), without any evidence of a "threshold" in this range below which a lower cholesterol is not associated with a lower risk^{6,7} (Figure 2).

Observational relationship between blood cholesterol levels and CHD risk: 1 mmol/l PROLONGED difference in blood cholesterol corresponds to about 50% less CHD

In these observational studies, the continuous relationship between CHD risk plotted on a doubling scale and blood cholesterol level is roughly linear. This implies that the **proportional** reduction in CHD risk associated with a particular prolonged absolute cholesterol difference is similar throughout the range above about 3 mmol/l. So, for example, a **prolonged** difference of about 1 mmol/l in blood cholesterol corresponds to about 50% less CHD, irrespective of the baseline cholesterol level (Figure 3). It also implies that a greater absolute cholesterol difference would be associated with the same greater proportional reduction in risk throughout this cholesterol range. For example, a prolonged cholesterol difference of 2 mmol/l rather than 1 mmol/l corresponds to about 75% rather than 50% less CHD, again irrespective of baseline blood cholesterol level (Figure 3).

Hence, the **absolute** size of the reduction in CHD produced by lowering blood cholesterol levels may be determined more by the combination of the absolute reduction in cholesterol and an individual's overall risk of CHD, than by just their initial cholesterol level. More intensive cholesterol-lowering regimens than are currently standard would be expected to produce greater reductions in CHD. Such benefits could be worthwhile not only among certain "hypercholesterolaemic" individuals but also among those who, although considered to have "normal" Western blood cholesterol levels, are for some other reason at particularly high risk (e.g. those with a history of myocardial infarction [MI]).

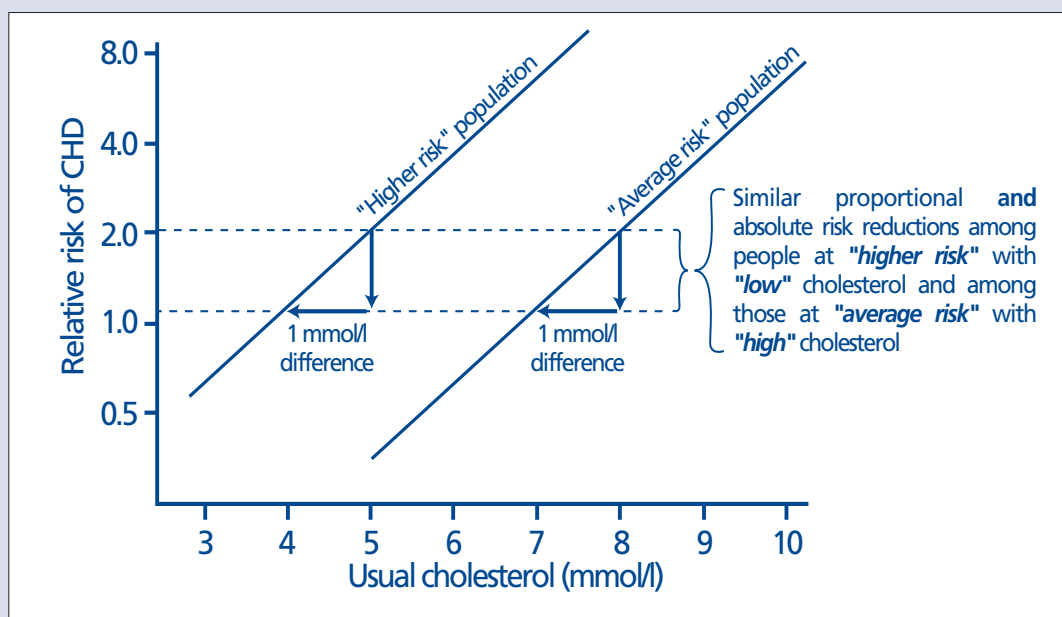


Figure 3: Greater absolute reductions in CHD risk with greater blood cholesterol reductions in individuals at greater absolute risk^{1,2}

Modest effects on CHD in randomised trials of treatments that lowered blood cholesterol by only about 10%

Earlier randomised controlled trials of drugs or diets involved an average blood cholesterol difference of only about 10%, and this was maintained for an average of only about 4 years. The observational studies suggest that such a difference in Western blood cholesterol levels that has persisted for decades eventually yields about a 30% difference in CHD. Overall, the results of these earlier randomised controlled trials indicate that, within just a few years of lowering blood cholesterol, CHD was reduced by at least half as much as expected from a long-term 10% difference in blood cholesterol levels⁸⁻¹⁰. More prolonged

treatments resulted in larger CHD reductions, with the trials that lasted 5-7 years producing a highly significant $22\% \pm 3$ CHD reduction⁸⁻¹⁰ — that is, about two-thirds of the reduction associated epidemiologically with a prolonged 10% cholesterol difference. Moreover, the studies of treatments that produced somewhat larger cholesterol reductions appeared to produce somewhat larger CHD reductions⁸⁻¹⁰.

Experience with HMG CoA reductase inhibitors (“statins”): greater blood cholesterol reductions appear to produce greater CHD reductions

By contrast with the cholesterol-lowering drugs and diets studied in those earlier trials, the HMG CoA reductase inhibitors (“statins”: such as simvastatin, lovastatin, pravastatin, fluvastatin and atorvastatin) are well-tolerated and produce substantial lowering of blood LDL-cholesterol (i.e. 1-2 mmol/l) and triglyceride (0.5 mmol/l), along with small increases in HDL-cholesterol¹¹⁻¹³. Recently, the results from some large-scale randomised trials of statin therapy among individuals at elevated risk of CHD have become available. The larger blood cholesterol reductions produced by the statins in those studies appeared to result in larger reductions in CHD than had been observed in previous trials of less effective cholesterol-lowering regimens.

In the Scandinavian Simvastatin Survival Study (4S), about 4000 patients at very high risk of CHD (about 80% had a history of previous MI) were randomly allocated to receive 20-40 mg daily simvastatin or placebo for 5 years^{14,15}. An average 1.7 mmol/l reduction in blood total cholesterol with simvastatin was associated with a highly significant reduction of about one-third in major coronary events (19% simvastatin-allocated vs 28% control: about 90 fewer such events per 1000 patients treated for 5 years). Like 4S, the Cholesterol And Recurrent Events (CARE) study involved about 4000 predominantly male patients with an average age of about 60, all of whom had a history of MI¹⁶. The 40 mg daily pravastatin regimen studied produced an average reduction in blood total cholesterol over the 5-year follow-up period of just over 1 mmol/l. Even though the entry blood cholesterol levels in the CARE study (average of about 5.5 mmol/l; all less than about 6.5 mmol/l) were quite a bit lower than those in 4S (average of 6.75; all between 5.5-8.0) and the cholesterol reduction was smaller, pravastatin was still associated with a clear reduction in CHD events of about one-quarter in this high-risk population (10% pravastatin-allocated vs 13% control: about 30 fewer per 1000 treated for 5 years).

In 4S, total mortality was significantly reduced by about one-third with simvastatin (182 simvastatin vs 256 control deaths: 95% CI of 15% to 42% reduction). But, despite there having been a similar number of deaths in the CARE study, the clear reduction in CHD events in that study was not translated into a significant improvement in survival (180 pravastatin vs 196 control deaths: 95% CI of 26% reduction to 12% increase). Although recent trials have not indicated an excess of non-CHD deaths or major morbidity (e.g. cancer incidence) with statin therapy¹⁴⁻¹⁷, even in aggregate they were not large enough¹⁸⁻²⁰ to rule out the sort of excesses (i.e. about 20-30%) that some reviewers have suggested might be produced by cholesterol-lowering therapy^{10,21,22}. Current studies, including the very large MRC/BHF Heart Protection Study of 40 mg daily simvastatin versus placebo²³, should help to resolve many of the remaining uncertainties as to whether any adverse effects of cholesterol-lowering treatment outweigh the CHD benefits in a wide range of patients at elevated risk of CHD^{18,19}.

Experience with higher-dose statin regimens

4S does provide clear evidence of worthwhile survival benefits with statin therapy in some types of very high-risk patients (e.g. post-MI middle-aged men with above-average blood cholesterol levels), and many such patients are now being treated routinely. But, even with standard-dose statin regimens, such patients are still at elevated risk of CHD. For example, about one-fifth of the patients allocated simvastatin in 4S still had major CHD events during 5 years of follow-up. As discussed earlier, observational epidemiological studies indicate that a lower risk of CHD is associated with a lower blood cholesterol level down at least to 3 mmol/l¹⁻⁷. In both 4S and the CARE study, the proportional reductions in CHD risk with statin therapy among patients with lower than average cholesterol levels at baseline were similar to those among patients with higher than average levels¹⁴⁻¹⁶. (Although little effect on CHD was observed among patients in the lowest third of baseline cholesterol in the CARE study, this subgroup — which was retrospectively selected for emphasis — included only a small number of events and the observation was consistent with the overall CHD reduction in CARE.) Direct randomised evidence of the effects on CHD of a larger cholesterol reduction than that produced by standard-dose statin regimens is, however, lacking.

Substantial effects on blood lipid levels of higher-dose regimens: The effects of higher-dose simvastatin regimens on blood cholesterol levels have been assessed. In a 26-week double-blind randomised crossover study among 156 subjects, the median reductions in blood total cholesterol were 30% (2.2 mmol/l) with 40 mg, 35% (2.6 mmol/l) with 80 mg, and 40% (2.9 mmol/l) with 160 mg daily simvastatin²⁴. The higher doses also produced much greater reductions in LDL-cholesterol (41% vs 47% vs 53%) and in triglycerides (21% vs 23% vs 33%), with similar increases in HDL-cholesterol (6% vs 7% vs 8%). These results are consistent with previous studies of lower-dose regimens, in which doubling the dose produced additional absolute reductions in blood LDL-cholesterol of about 6%²⁵, indicating that there is a linear log-dose response relationship at least up to 160 mg simvastatin daily. (The reduction in blood LDL-cholesterol observed with 80-160 mg daily simvastatin is comparable to that observed with the combination of standard simvastatin regimens and a bile acid sequestrant, and with the highest doses studied [40-80 mg daily] of a newer statin, atorvastatin^{12,26}.)

Higher-dose regimens appear to be well tolerated, with few short-term side-effects: Previous clinical trial experience of prolonged treatment in tens of thousands of patients suggests that the statins are remarkably well tolerated, with few side-effects^{14-17,23}. Marked elevations of liver enzymes (alanine transaminase [ALT] and aspartate transaminase [AST]) have not been observed significantly more commonly among patients allocated several years of standard-dose regimens (e.g. 20-40 mg simvastatin or 40 mg pravastatin daily) than among those allocated placebo in the large randomised trials^{14-17,23}. Moreover, where such elevations have been observed in association with statin therapy, they have usually been reversible. Like other cholesterol-lowering drugs (such as fibrates), statin regimens have been reported to produce elevations of creatine kinase (CK) associated with muscle pain or weakness. But, in the large randomised trials of standard-dose regimens, no significant excesses of elevated CK with muscle symptoms were observed among those allocated statin therapy. When elevated CK and/or muscle symptoms have been observed with standard regimens of statin therapy, this has generally resolved without stopping treatment, and in only very few cases has it progressed to significant myopathy.

In a short-term study of higher-dose simvastatin regimens among 156 subjects, there were dose-related increases in the average levels of transaminases (ALT and AST) and of CK²⁴. No elevations of transaminases above 3x the upper limit of normal [ULN] were observed on 40 mg daily simvastatin, but one case occurred on 80 mg and two on 160 mg. A single case of myopathy (defined according to standard criteria as unexplained muscle pain or weakness with CK >10x ULN) was observed on 160 mg daily, but this resolved without incident following discontinuation of simvastatin. No significant differences between these dose regimens were observed in any other laboratory measures (including steroid hormones), or in other possible adverse events.

SEARCH: to determine whether larger blood cholesterol reductions produce larger, and worthwhile, CHD reductions in high-risk individuals

This Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) aims to demonstrate reliably whether a more intensive cholesterol-lowering regimen produces a greater reduction in CHD than does a standard regimen, without an unacceptable level of adverse effects. In a long-term trial in high-risk individuals of 80 mg daily simvastatin versus a standard 20 mg daily simvastatin regimen, it should be possible to achieve an average difference in total and LDL-cholesterol of at least 0.5 mmol/l. The epidemiological and trial evidence suggest that such a difference maintained for about 5 years might well produce at least a 15-20% further reduction in CHD. Patients who have had a previous MI are at very substantially increased absolute risk of coronary events, even with standard statin regimens, so even a moderate further proportional reduction in CHD risk could, in absolute terms, be very worthwhile (especially if any excess of adverse effects with more intensive regimens is shown to be comparatively small). In order to be able to detect a 15-20% further CHD reduction in such patients, about 12,000 MI survivors in whom statin therapy is considered to be clearly indicated are to be randomly allocated to receive 80 mg daily simvastatin versus 20 mg daily simvastatin for about 5 years (see Section 2.4 for statistical power calculations). Long-term experience with high-dose statin regimens is limited, and so SEARCH will assess carefully not only efficacy but also any major long-term side-effects (see section 2.5 for safety monitoring).

1.2 RELIABLE ASSESSMENT OF THE EFFECTS OF REDUCING BLOOD HOMOCYSTEINE LEVELS BY FOLIC ACID PLUS VITAMIN B₁₂ THERAPY

Homocysteine metabolism and risk of occlusive vascular disease

Patients with the rare autosomal recessive condition homocystinuria have extremely high blood levels of total homocysteine, and a high incidence of occlusive vascular disease in adolescence and, even, in childhood^{27,28}. Homocysteine is a sulphur-containing amino acid derived from methionine that can be metabolised by one of two enzymatic pathways: re-methylation to methionine by methylenetetrahydrofolate reductase (MTHFR) or trans-sulphuration to cystathionine by cystathionine beta-synthase (CBS)²⁹. Homocystinuria results from several genetic defects in the enzymes MTHFR or CBS²⁸, but premature vascular disease develops irrespective of the site of metabolic deletion, suggesting that homocysteine is responsible for the vascular damage^{30,31}.

Blood levels of homocysteine can also be moderately elevated in those individuals who are heterozygous for these enzymatic defects, or in those with inadequate intake of folic acid and vitamins B₆ and B₁₂, which are co-factors in the enzymatic pathways of homocysteine metabolism. Basal levels of blood homocysteine are determined

predominantly by the re-methylation pathway, which is dependent on folic acid and vitamin B₁₂, while homocysteine levels after a methionine load are determined predominantly by the trans-sulphuration pathway, which uses vitamin B₆ as a co-factor²⁹. Dietary supplementation with these vitamins is an integral part of the treatment of homocystinuria. The relative contribution of genetic and nutritional factors to plasma homocysteine levels, and vascular disease risk, in the general population is uncertain^{28,32-35}.

Epidemiological associations between elevated blood homocysteine levels and occlusive vascular disease

There is consistent evidence from a large number of cross-sectional, case-control and prospective observational studies conducted in different settings of a positive association between blood levels of total homocysteine and the risk of occlusive vascular disease³⁴⁻⁴². Throughout the range of blood homocysteine levels studied (i.e. about 8 to 15 $\mu\text{mol/l}$), epidemiological studies have indicated that higher blood homocysteine levels are significantly associated with an increased risk of CHD, both in men and in women (Figure 4). Higher blood homocysteine levels have also been associated with increased risks of cerebrovascular disease and of peripheral arterial disease.

Taken together, the epidemiological evidence supports a graded response, as for cholesterol, with no threshold level above at least about 8 $\mu\text{mol/l}$ below which lower blood homocysteine is not associated with lower vascular disease risk. Consequently, throughout this range, a prolonged 5 $\mu\text{mol/l}$ lower baseline blood homocysteine level appears to be associated with a lower vascular disease risk of about one-third. Studies of the association of vascular risk with blood homocysteine levels measured just at baseline may, however, under-estimate the strength of the association with "usual" blood homocysteine levels because an individual's homocysteine level varies to some extent. After correction for this "regression dilution" bias⁶, a prolonged lower "usual" blood homocysteine of only about 3-4 $\mu\text{mol/l}$ might, therefore, correspond to about one-third less vascular disease.

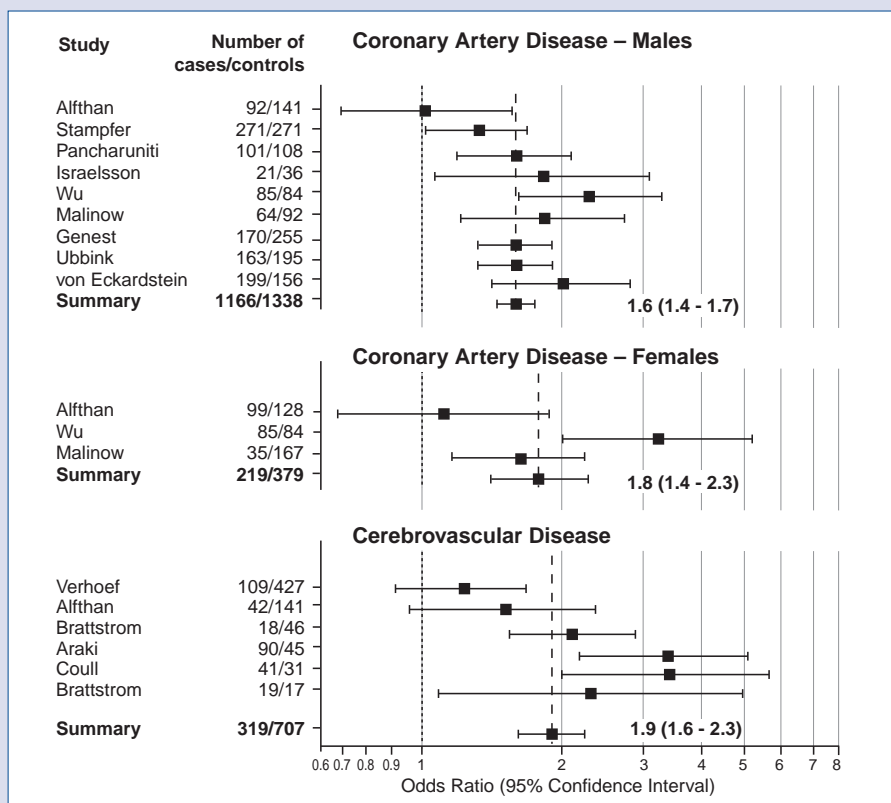


FIGURE 4: Relative risk of vascular disease associated with 5 $\mu\text{mol/l}$ difference in baseline blood homocysteine level: meta-analysis of observational studies³⁴

Evidence for a causal link between blood homocysteine levels and occlusive vascular disease

Several lines of evidence suggest that the association of blood homocysteine levels with occlusive vascular disease may represent a cause-and-effect relationship. A variety of genetic and environmental factors can lead to elevated plasma homocysteine levels, but the relationship with vascular disease appears to be present regardless of the cause of elevated homocysteine levels. Plausible biological mechanisms for a causal relationship have been proposed³⁵. Homocysteine has been shown to have a direct toxic effect on vascular endothelium⁴³, to stimulate the proliferation of smooth muscle cells⁴⁴, consistent with early atherosclerotic lesions, and to cause oxidation of LDL-cholesterol⁴⁵. It has also been reported to have various effects on vascular haemostatic properties, including decreasing expression of thrombomodulin and inhibiting protein C activation, which might contribute to the development of thrombosis⁴⁶.

Cross-sectional and case-control studies cannot rule out the possibility that vascular disease itself may have altered homocysteine levels, but similar associations have been observed in prospective studies in which blood was taken some years before vascular disease was diagnosed³⁴. Elevated homocysteine levels precede not only the occurrence of vascular events but are also associated with early signs of carotid artery thickening and stenosis^{37,38}, and with subsequent mortality in patients with established coronary disease⁴². Despite modest correlations between blood homocysteine and other risk factors (e.g. increased age, smoking, blood cholesterol and blood pressure, and decreased physical activity)⁴⁷, homocysteine appears to be an independent risk factor for occlusive vascular disease.

Reducing blood homocysteine levels by folic acid plus vitamin B₁₂ therapy

Blood homocysteine levels are strongly and inversely correlated with plasma levels of folate, and there is some evidence of weaker inverse associations with vitamin B₆ and B₁₂ levels^{48,49}. Concentrations of blood homocysteine decline progressively until daily dietary folate intakes exceed about 400 µg/day, and plasma folate reaches about 15 nmol/l³⁴. About half of the subjects in the Framingham study cohort had plasma folate concentrations below about 9 nmol/l⁴⁹, and US national data from the late 1980s indicated that about 90% of adults consumed less than 400 µg/day of folic acid⁵⁰. The 1990 UK National Food Survey indicated that the average folate intake of adults was even lower (240 µg/day)^{51,52} than in the US, which suggests that dietary folate supplementation would reduce blood homocysteine levels in almost all UK adults.

Consistent with the observational evidence, randomised trials indicate that dietary intake of folic acid has the dominant effect on lowering blood homocysteine levels^{34,35,53}. Vitamin B₁₂ supplementation may have a small additional homocysteine-lowering effect, but vitamin B₆ appears to have little or no effect on fasting homocysteine levels (although it does reduce levels after a methionine load and perhaps, by extrapolation, after meals)⁵³. Taken together, the randomised trials of different dose regimens suggest that daily treatment with 1-5 mg folic acid and 0.5-1 mg vitamin B₁₂ would produce a long-term average reduction in blood homocysteine of about 3-4 µmol/l (for example, from about 12-13 µmol/l to about 9-10 µmol/l in patients with pre-existing CHD)^{34,53}.

SEARCH: an opportunity to obtain substantial randomised controlled evidence about the effects of homocysteine-lowering therapy on vascular disease

There is, as yet, very little randomised controlled evidence about the effects on vascular disease of lowering blood homocysteine levels⁵⁴. If, as for cholesterol-lowering, much of the lower risk of occlusive vascular disease associated epidemiologically with lower blood homocysteine levels appears within just a few years then an average reduction of about 3-4 $\mu\text{mol/l}$ maintained for 5 years might produce at least a 15-20% reduction in CHD. Among at least 12,000 individuals at very high risk of CHD, SEARCH provides an excellent opportunity to obtain substantial evidence about such effects by randomly allocating not only simvastatin dose but also homocysteine-lowering therapy versus placebo in a "2 x 2 factorial" design (see Section 2.2).

SEARCH will, therefore, compare a daily dose of 2 mg folic acid plus 1 mg vitamin B₁₂ versus matching placebo for about 5 years. Addition of this dose of vitamin B₁₂ to folic acid should not only produce some additional reduction in plasma homocysteine levels, but it will also avoid the theoretical risk of neuropathy due to unopposed folic acid in vitamin B₁₂ deficient patients, even those with intrinsic factor deficiency or other malabsorption states⁵⁵⁻⁵⁸. The factorial design of SEARCH will allow **all** randomised patients to contribute **fully** to assessment of the separate effects of statin dose and of homocysteine-lowering therapy, without any material increase in the sample size or non-drug cost beyond that required for a study that just assessed statin dose⁵⁹. As well as increasing the scientific interest of the trial, assessment of folic acid plus vitamin B₁₂ should make the study of even greater interest to participating patients.

2. SEARCH: PLAN OF INVESTIGATION

2.1 AIMS

The primary objectives of SEARCH are to assess, in high-risk patients, the effects on the incidence of total (i.e. fatal or not) CHD events during the scheduled treatment period of:

- (i) the greater reduction in blood cholesterol produced by the higher simvastatin dose regimen; *and*
- (ii) the reduction in blood homocysteine produced by folic acid plus vitamin B₁₂.

Secondary objectives include assessment of the effects of the study treatments on total and fatal CHD in particular subgroups, and assessment of their effects on total and cause-specific mortality and on the incidence of cancer, strokes, major vascular procedures and other conditions that require hospitalisation (see Section 2.3).

2.2 TREATMENT COMPARISONS

Run-in period prior to randomisation

Prior to randomisation, potentially eligible patients (see Section 3.1) are to enter a Run-in period during which they will receive 20 mg daily simvastatin and placebo-vitamin tablets for up to 2 months. The Run-in period of about 2 months prior to randomisation is to help ensure that only those likely to continue taking study treatment for an extended period are randomised. Any patients who appear to be non-compliant or who wish to drop out for any reason during this Run-in period are not to be randomised. Also, the patient's own doctor may decide during Run-in that the patient should not be randomised (see Section 3.2). Patients are to be randomised only if, at the end of the Run-in period, they seem likely to comply with the study protocol for several more years. By this process, many potential drop-outs should be excluded before becoming part of the randomised comparison, with a consequent improvement in statistical sensitivity of the "intention-to-treat" analyses⁵⁹.

Random allocation of higher-dose versus standard-dose simvastatin, and folic acid plus vitamin B₁₂ versus placebo

Eligible patients will be randomised in a 2 x 2 factorial blinded design between:

- Higher-dose (80 mg daily) versus standard-dose (20 mg daily) simvastatin, and
- Folic acid (2 mg daily) plus vitamin B₁₂ (1 mg daily) versus placebo.

Calendar-packed study treatment is to be taken each evening for about 5 years unless some clear reason to stop develops. For the comparison of simvastatin doses, a double-dummy method is being used since the 80 mg tablet and the 20 mg tablet differ in appearance. Randomised patients will, therefore, be allocated either one 80 mg active-simvastatin tablet plus one 20 mg placebo-simvastatin tablet or one 20 mg active-simvastatin tablet plus one 80 mg placebo-simvastatin tablet daily. In addition, they will be allocated a single tablet daily containing either 2 mg folic acid plus 1 mg vitamin B₁₂ or matching placebo.

Full efficiency of 2 x 2 factorial design: separate assessment of both study questions without any material effect on non-drug cost or sample size requirements

A 2 x 2 factorial design assessing the effects of lowering blood homocysteine will not prevent reliable assessment of the effects of lowering blood cholesterol to different extents with different simvastatin doses (or vice versa). For, outcome among all the patients allocated higher-dose simvastatin can still be compared with that among all those allocated standard-dose simvastatin (even though half of each group will have received folic acid plus vitamin B₁₂: Figure 5).

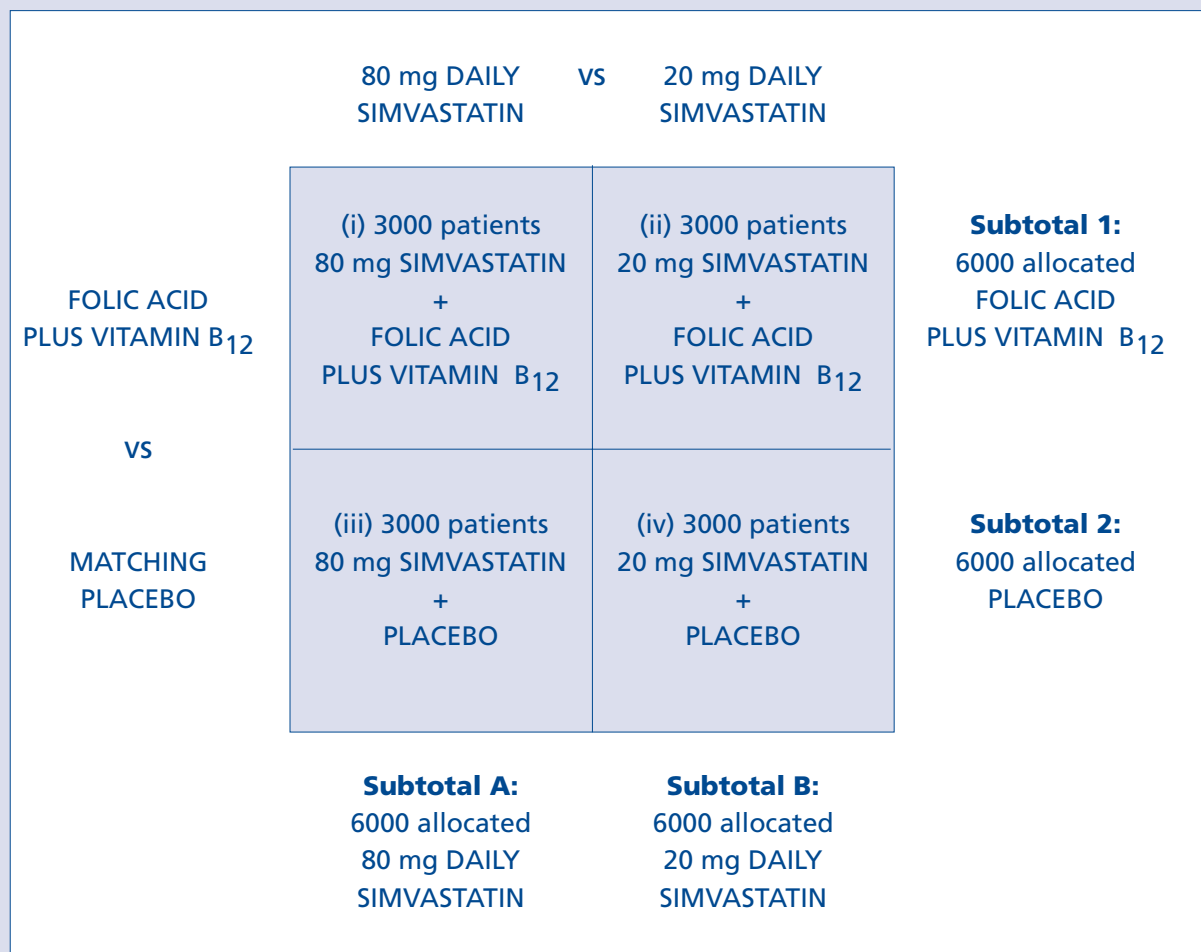


FIGURE 5: Factorial design involving 12,000 patients

The main assessment of the effects of different doses of simvastatin will involve comparing the outcomes among all 6000 patients allocated 80 mg daily simvastatin (subtotal A) versus those among all 6000 allocated 20 mg daily simvastatin (subtotal B). Similarly, the main assessment of the effects of folic acid plus vitamin B₁₂ will involve comparing the outcomes among subtotals 1 and 2. Use of such a factorial design instead of a simple 2-way design has little or no effect on the statistical sensitivity with which the overall benefits of different simvastatin doses (or of folic acid plus vitamin B₁₂) can be assessed, or on the total number of patients required in the study⁵⁹.

2.3 ASSESSMENT OF OUTCOME

Primary assessments

Statin therapy: the **primary** comparison will involve “logrank” analyses⁵⁹ of **total CHD events** (defined as fatal CHD [ICD 410-414 in the 9th International Classification of Diseases], non-fatal MI or coronary revascularisation procedures [i.e. coronary artery grafts or coronary angioplasty]) during the scheduled treatment period among all those allocated 80 mg daily simvastatin versus all those allocated 20 mg daily simvastatin.

Folate-based therapy: the **primary** comparison will involve “log-rank” analyses of **total CHD events** during the scheduled treatment period among all those allocated folic acid plus vitamin B₁₂ versus all those allocated placebo.

Secondary assessments

The principal subsidiary comparisons will be of the effects of (i) simvastatin dose allocation and (ii) folic acid plus vitamin B₁₂ allocation on total CHD separately in the first year after randomisation and in the later years of the scheduled treatment period, to see if any protective effects increase with time.

Other subsidiary comparisons will be made of the effects during the scheduled treatment period:

- (i) on total CHD of simvastatin dose allocation among patients subdivided into 3 similar-sized groups with respect to blood cholesterol levels at the end of the pre-randomisation Run-in period on 20 mg daily simvastatin;
- (ii) on total CHD of folic acid plus vitamin B₁₂ allocation among patients subdivided into 3 similar-sized groups with respect to (a) plasma folate levels and (b) blood homocysteine levels at the end of the pre-randomisation Run-in period on placebo-vitamins;
- (iii) on total CHD of each study treatment in the presence and the absence of the other study treatment allocation; and
- (iv) on total strokes of (a) simvastatin dose allocation and (b) folic acid plus vitamin B₁₂ allocation.

Tertiary assessments

In addition, comparisons will be made of the effects during the scheduled treatment period of each of the study treatment allocations on total and cause-specific (CHD and non-CHD) mortality; fatal CHD excluding the first year after randomisation; coronary revascularisations (i.e. CABG and PTCA); haemorrhagic and other strokes; venous thromboembolism; total and site-specific cancers; hospitalisations for various causes; and possible adverse effects of treatment.

2.4 SAMPLE SIZE AND PREDICTED NUMBER OF EVENTS

At least 1900 CHD events among 12,000 individuals at very high risk of CHD

If the greater reduction in blood total and LDL-cholesterol levels (i.e. an average of at least 0.5 mmol/l) expected with 80 mg daily simvastatin, compared with 20 mg daily simvastatin^{24, 25}, translates into at least a 20% further reduction in CHD, then a study involving at least 1900 CHD events provides an excellent chance of demonstrating an effect on CHD at a convincing level of statistical significance (see Table). Indeed, such a study would still have good power to detect a somewhat smaller reduction in CHD. Similarly, if the 3-4 µmol/l reduction in blood total homocysteine levels expected with the folate-based therapy being studied produces a 15-20% CHD reduction, this too could be detected reliably (with no material effect on the simvastatin comparison⁵⁹).

TABLE: Predicted power to detect 15-20% reductions in CHD

Proportional reduction to detect	No. of events (and %) during 4-5 years		Events prevented per 1000	Approximate power at 2P<0.01
	Control	Intervention		
20%	1070 (17.8%)	850 (14.2%)	36	>99%
15%	1040 (17.3%)	880 (14.7%)	26	90%

Previous studies in patients with a history of MI suggest that, in patients receiving the standard 20 mg daily simvastatin regimen, the annual rate of CHD death plus non-fatal MI and coronary revascularisation procedures would be about 4%¹⁴⁻¹⁶. Additional reductions of 15-20% among such high-risk patients would correspond to substantial absolute benefits (see Table): for example, they would be similar in size to those observed with the use of statin therapy in the CARE study¹⁶. If such differences exist then a trial of about 12,000 post-MI patients with at least 4 years of follow-up should be able to detect them reliably. SEARCH is designed, therefore, to continue for a minimum of 4 years median follow-up until a total of at least 1900 patients have had confirmed CHD events. The Steering Committee will review the blinded CHD event rate during follow-up and the differences in blood cholesterol and homocysteine observed annually between the respective treatment groups. Based on this information, the Steering Committee may modify the scheduled number of randomised patients or CHD events, or the study duration. Moreover, the Steering Committee can decide to stop the study early in the light of recommendations from the independent Data Monitoring Committee (see Section 2.5).

2.5 DATA AND SAFETY MONITORING

Interim analyses: role of the Data Monitoring Committee and Steering Committee

During the period of the study, unblinded interim analyses of mortality, of CHD events and of any other information that is available on major events (including serious adverse events), along with any other analyses requested, will be supplied at least annually, in strict confidence, to the chairman of the independent Data Monitoring Committee. In the light of these analyses and the results of any other relevant trials, the Data Monitoring Committee will advise the Steering Committee if, in their view, the randomised comparisons in SEARCH have provided **both** (a) “proof beyond reasonable doubt”^{*} that for all patients, or for some specific types, really prolonged use of higher-dose simvastatin or of folate-based therapy is clearly indicated or clearly contraindicated in terms of a net difference in all-cause mortality, **and** (b) evidence that might reasonably be expected to influence materially the patient management of many clinicians who are already aware of any other main trial results. The Steering Committee can then decide whether to modify the study (or to seek extra data).

Unless this happens, the Steering Committee, the collaborators, Merck Sharp & Dohme and the coordinating centre staff (except those who supply the confidential analyses) will remain ignorant of the interim results on mortality and morbidity until the study is terminated. Collaborators, and all others associated with the study, may write (preferably through the Oxford coordinating centre) to the chairman of the Data Monitoring Committee, drawing attention to any worries they may have about the possibility of particular side-effects, or about particular categories of patient requiring special consideration, or about any other matters that may be relevant.

Monitoring of any serious adverse experiences believed to be due to study treatment

Throughout the trial, all **serious adverse experiences** believed with a reasonable probability to be due to study treatment** are to be reported immediately by telephoning the 24-hour telephone service (see Section 3.6). During this telephone call, standard information (i.e. identity of the patient and of the person reporting the event, nature and date of event, and reasons for attribution to study treatment) will be recorded directly on the coordinating centre computer. These reports will be reviewed immediately, blind to treatment allocation, by the clinical coordinators, and any further information required sought urgently. Confirmed reports will then be promptly forwarded “unblinded” to the chairman of the Data Monitoring Committee, and “blinded” to the chairman of the South Thames Multicentre Research Ethics Committee and to Merck Sharp & Dohme in Hoddesdon. The company will notify the coordinating centre at the Clinical Trial Service Unit if any further information is needed (including unblinding) and will then forward such reports to any relevant drug regulatory agencies.

* Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but in general a difference of **at least 3** standard deviations in an interim analysis of a major endpoint would be needed to justify halting, or modifying, such a study prematurely, especially if the comparison was based on relatively few events (e.g. less than 100). If this criterion were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance, and so no fixed schedule is proposed⁵⁹.

** “Serious” adverse experiences are defined as those which result in death or are life-threatening, produce a persistent or significant disability, require in-patient hospitalisation or the prolongation of existing hospitalisation, are cancer or congenital abnormality, or are judged to jeopardise the patient or to require intervention to prevent any of the other outcomes listed.

Serious adverse experiences that are **not** thought to be due to study treatment are **not** to be reported in this way. All such events will, however, be routinely recorded at follow-up visits and will be monitored centrally as the trial progresses.

2.6 CENTRAL COORDINATION AND COLLABORATING CLINICS

Central coordination by the Clinical Trial Service Unit

The Clinical Trial Service Unit (CTSU) at Oxford University is coordinating this study. It is responsible for obtaining Multicentre Research Ethics Committee approval; for the training and monitoring of all staff directly involved in the study; for the supply of conveniently packaged study drugs and other study materials; for the identification, with the assistance of the local medical collaborators and study clinic staff, of potentially eligible patients; for obtaining permission to invite suitable patients to each study clinic; for the initial invitation of patients to Screening clinics and for allocation of subsequent clinic appointments; for the provision of a 24-hour Freefone telephone service (for appointment changes, central randomisations, urgent queries, unblinding when medically necessary, and reporting of any serious adverse experiences believed to be due to study treatment); and for the collection and analysis of data and blood samples. (This is summarised below, and is described in detail in the Hospital Manual and in the coordinating centre operating procedures.)

Training and monitoring: Clinic staff will be trained by the Oxford coordinating centre in correct study clinic procedures (as summarised in Section 3 of the protocol and described in detail in the Hospital Manual). Coordinating centre staff will visit each collaborating clinic 2-3 times during the first year of the study to discuss the study rationale and design with relevant clinical and other staff, to assist in the setting up of study clinics, and to monitor the conduct of the clinics during the Screening and Randomisation phases. Subsequently, 1-2 visits will be made each year to monitor the Follow-up clinics and to help resolve any issues that may have arisen. The coordinating centre staff will also arrange regular meetings of all the collaborators and of all the clinic staff to discuss the progress of the study and other general issues, and to provide an update on the results of any other relevant studies. The Oxford coordinating centre staff will maintain regular contact with the local clinic staff and medical collaborators between visits and meetings. Collaborators and clinic staff will be encouraged to contact the coordinating centre office (or 24-hour telephone service for urgent queries) if they wish to discuss some problem or other issue related to the study.

Supply of study materials: Equipment required for the study clinics (e.g. weighing scales, facsimile machines for rapid communication with the coordinating centre, etc) and all consumables (e.g. study manuals and forms, stationery, blood sampling tubes and needles, etc) will be provided by the coordinating centre. All study medication will be supplied in treatment packs containing the appropriate number of calendar blister-strips for each period of the study. Any study drug not required by participating patients is to be collected by clinic staff and returned at regular intervals to the coordinating centre for disposal.

Data handling: Lists of potentially eligible patients will be sought from hospital and other medical records, preferably in computerised format, by the Oxford coordinating centre. This information will be used by the coordinating centre to generate invitations, in the name of the local medical collaborator, for patients to attend local study clinics (see Section 3.1). The top copies of all completed and signed clinic forms (except those

Screening Forms with consent pending: see Sections 3.2 to 3.5) are to be sent to the coordinating centre at the end of each clinic day (with the middle copies kept in the patients' study files in each study clinic and, if required, the bottom copies used for pharmacy records). The information on these forms will, where necessary, be coded by the coordinating centre staff and then entered onto the coordinating centre computer (following an operating procedure for data handling, in accordance with Good Clinical Practice guidelines).

Any missed Follow-up clinic appointments identified by the coordinating centre will result in checks that the study nurse has arranged another appointment (or, if the patient is definitely no longer willing to attend clinic, that a telephone follow-up will be conducted). Errors in the completion of study forms detected by the coordinating centre will result in computer-generated correction requests being sent to the clinic staff for completion, with all such corrections to the data being entered on the central computer. The coordinating centre is responsible for seeking confirmation and additional information about any relevant clinical events reported during follow-up, and for obtaining details from national registries of any deaths or non-fatal cancers among study patients (see Section 3.7).

Laboratory: Blood samples taken by the clinic staff from those patients who agree to start Run-in treatment at the initial Screening visit or at a subsequent Consent Pending visit, and samples taken from all randomised patients attending each subsequent clinic visit, are to be picked up by couriers at the end of each clinic day for overnight delivery to the coordinating centre laboratory in Oxford. The central laboratory will use part of each blood sample for immediate assays, with the remainder of certain samples being frozen for subsequent assays (see Sections 3.2 to 3.5). The laboratory uses a number of internal and external quality control procedures and follows a standard operating procedure (in accordance with Good Laboratory Practice guidelines). Checked assay results will be transferred to the central computer and linked to the patient's other data. The coordinating centre will inform the patient's general practitioner, and the clinic staff, of the routine Screening and Randomisation visit results (see Sections 3.2 and 3.3). Subsequently, for patients starting study treatment, any biochemical abnormalities requiring action will be reported back to the clinic staff and, in such cases, appropriate Early Recall visit arrangements will be made with the patient by the coordinating centre (see Section 3.5).

Source documents and archiving: The lists of potentially eligible patients provided to the Oxford coordinating centre, the clinic visit records, the computer-generated error forms, the additional information obtained on reported outcome measures and other relevant events, the death certificates, the blood assay results and the drug supply records constitute the "source documents" for the study. The coordinating centre will retain these data and records for at least 15 years. Merck Sharp & Dohme and regulatory agencies will have the right, in accordance with Good Clinical Practice guidelines, to commission a confidential audit of such records kept in the coordinating centre and in the collaborating clinics, as long as this does not result in unblinding of the interim results while the study is still in progress.

Organisation of study clinics in collaborating hospitals

About 80-100 clinics each randomising about 150 patients: Experience in the ongoing MRC/BHF Heart Protection Study²³ indicates that, for each collaborating clinic to

randomise 150 patients in the present study, several thousand patients with a history of previous MI who are already being treated with a statin (or in whom such therapy is considered clearly indicated) need to be identified. This should yield about 1000 potentially eligible patients who can be invited to the local Screening clinic, of whom about 500 patients are likely to attend. These clinic attendees can then be screened over a 12-18 month period in the equivalent of about five 3-hour clinic sessions each week. Subsequent follow-up of the 150 randomised patients this would yield requires only about two 3-hour clinic sessions weekly. Hence, about 80-100 collaborating clinics (or equivalent, since a particular clinic might be able to randomise more than, or less than, 150 patients) should be able to randomise and follow about 12,000 patients.

Setting up study clinics: The medical collaborator(s) in each hospital is responsible, with the help of the Oxford coordinating centre, for obtaining local ethics committee approval; for assisting in the identification of potentially eligible patients (including liaison with hospital medical records staff); for appointing and overseeing the clinic staff; and for ensuring that adequate clinic and reception space is available. The equivalent of one half-time experienced nurse is required during the first 18 months for the Screening of about 500 patients (with centres screening fewer patients requiring fewer hours of clinic time). A part-time receptionist/secretary covering the hours of clinic time will ensure efficient running of the Screening programme (including confirmation of personal details and appointments, and handling paper work). During the follow-up period, the equivalent of one day per week of nurse time should be sufficient to see 150 randomised patients at 2, 4, 8 and 12 months in the first year, and subsequently at 6-monthly intervals, to monitor and deal with any possible adverse drug effects, to record any clinical study end-points, and to encourage compliance.

Source of support and non-negligent liability cover

Independence of study from source of support: The study is being funded by a grant to the University of Oxford from Merck Sharp & Dohme (the manufacturers of simvastatin). It has, however, been designed and will be conducted, analysed and interpreted by CTSU independently of this source of support, which has no representative in its organisation and will, like the Steering Committee, remain blind to the main results as they accumulate. This arrangement is intended to ensure that no suggestions of lack of objectivity of the findings can be justified. The study has been designed to comply with the principles of the Declaration of Helsinki (as amended in 1989).

Non-negligent liability: Merck Sharp & Dohme has agreed to indemnify, and hold harmless, any institution or individual collaborating in the study from and against any and all claims or law suits resulting from participation, provided that (i) those seeking indemnity have not departed in any importantly relevant manner from compliance with the protocol, and provide all reasonably possible assistance to Merck in defence of such claims (allowing the company, if it wishes, to settle the claim or take over the defence), and (ii) the company will not be liable for any injuries resulting from medical negligence.

Publication in the names of all collaborators

The success of this study depends entirely on the wholehearted collaboration of a large number of doctors and nurses (and, of course, patients). For this reason, chief credit for the main results will be given not to the central organisers, but to all those who have collaborated in the study.

3. SUMMARY OF PRACTICAL PROCEDURES

(see Hospital Manual for details)

POTENTIALLY ELIGIBLE



- History of previous myocardial infarction
 - Male or female
 - Age: 18 to 75 years
 - Current use of any HMG CoA reductase inhibitor ("statin") or clear indication for statin
-

IDENTIFICATION & INVITATION



- Potentially eligible patients identified from medical records
 - Agreement to screen such patients sought from consultants and GPs
 - Patient invited to attend local Screening clinic appointment
-

SCREENING CLINIC VISIT (-2 months)



- Past medical history and other eligibility factors recorded on Screening Form
 - Height, weight and blood pressure recorded
 - Information on diet and risk factor modification given
 - Consent sought from eligible individuals with indication for statin therapy (and without clear contraindications to either study treatment)
 - Blood samples taken for central laboratory analysis
 - Run-in treatment pack (20 mg simvastatin tablet and placebo-vitamin tablet daily) given to eligible and consenting patient (and any non-study statin stopped)
 - Randomisation appointment made for 2 months later
 - GP informed of patient's lipid profile and biochemistry, and of entry in Run-in phase
-

RANDOMISATION CLINIC VISIT (0 months)



- Adverse events during Run-in and compliance recorded on Randomisation Form
 - Regular non-study treatment recorded
 - Final check of eligibility
 - Blood samples taken for central laboratory analysis and frozen storage
 - Randomisation by telephone call to Oxford coordinating centre:
0800-585323 (Freephone) or 01865-240972
 - Allocated Randomisation treatment pack given to patient:
— 80 mg simvastatin daily **vs** 20 mg simvastatin daily, and
— 2 mg folic acid plus 1 mg vitamin B₁₂ daily **vs** matching placebo
 - Follow-up appointment made for 2 months later
 - GP informed of patient's lipid profile and haematology, and of randomisation
-

FOLLOW-UP CLINIC VISITS at 2, 4, 8 & 12 months, then 6-monthly



- Vascular events, other serious adverse events and any adverse events considered to be due to study treatment recorded on Follow-up Form
 - Regular non-study treatment and compliance with study treatment recorded
 - Blood sample taken for central laboratory analysis of ALT and CK
 - Follow-up treatment pack given to patient and compliance encouraged
 - Next Follow-up appointment scheduled
 - Annual assessment of treatment effects on blood from random sample of patients
-

COORDINATING CENTRE MONITORING OF SAFETY AND EFFICACY

- Early Recall visits arranged, as required, to monitor biochemical or other problems
 - Further details of any relevant events reported sought from responsible clinicians
 - Flagging for mortality and cancer at central registries
-

3.1 ELIGIBILITY AND IDENTIFICATION OF SUITABLE PATIENTS

Eligibility for the study

Men or women aged between 18 and 75 years at the time of invitation for Screening are eligible for the study, provided they fulfil **all** of the following criteria:

- (1) **History of prior myocardial infarction:** The patient is considered to be at very substantial risk of having a CHD event over the next 5 years on the basis of a history of a definite or probable diagnosis of MI. (N.B. If MI, hospitalisation for angina, CABG or PTCA has occurred within the previous 3 months, or if a coronary revascularisation procedure is planned, then the patient would not be eligible but may be invited for a later repeat of the Screening visit.)
- (2) **Current use of any HMG CoA reductase inhibitor ("statin"), or clear indication for statin therapy:** The patient's own doctor has already started the patient on statin therapy, or considers such therapy to be clearly indicated.
- (3) **No clear indication for folic acid:** Neither the patient nor the patient's own doctor considers there to be any definite need for the patient to take folic acid routinely.
- (4) **No clear contraindications to the study treatments:** The patient's own doctor and the screening clinic staff do not consider there to be any clear contraindications to statins, folic acid or vitamin B₁₂. Contraindications for this study include:
 - Screening plasma total cholesterol <3.5 mmol/l in a patient already on statin therapy, or <4.5 mmol/l in a patient not already on such therapy;
 - Chronic liver disease (i.e. cirrhosis or hepatitis) or abnormal liver function (i.e. plasma ALT>1.5 x upper limit of normal [ULN]);
 - Severe renal disease or evidence of renal impairment (i.e. plasma creatinine >2xULN);
 - Inflammatory muscle disease (such as dermatomyositis or polymyositis) or CK >3xULN;
 - Concurrent treatment with cyclosporin (or a condition likely to result in organ transplantation and the need for cyclosporin), nefazodone (Dutonin), methotrexate, systemic azole antifungals or the macrolide antibiotics clarithromycin or erythromycin. (N.B. If such treatment is likely to be only temporary — as is likely to be the case, in particular, with macrolide antibiotic use — then the patient may be invited for a later repeat of the Screening visit.);
 - Concurrent treatment with fibrates or high-dose (over 1 g per day) niacin. (N.B. Patients on other cholesterol-lowering drugs or diets can still be entered in the trial, although they must be prepared to stop any non-study statin.);
 - Child-bearing potential (i.e. pre-menopausal woman who is not sterilised or using a reliable method of contraception).
- (5) **No other predominant medical problem:** The patient does not have some condition (other than CHD) that might limit compliance with 5 years of study treatment:
 - Recent history of alcohol or drug abuse;
 - Psychiatric disorder, senility, or physical disability (such as severely disabling stroke);

- Severe heart failure (i.e. causing shortness of breath at rest) or some importantly life-threatening condition other than vascular disease (i.e. life-expectancy of less than 5 years: such as very severe chronic airways disease; or any history of cancer, other than non-melanoma skin cancer).

Identification of potentially eligible patients and invitation to Screening Clinics

Potentially eligible post-MI patients will be identified by the Oxford coordinating centre from patient records. These include records of patient hospital discharges following MI and of statin prescriptions kept centrally by health authorities and collaborating hospitals, records kept for special clinics and wards (e.g. the coronary care unit) and records kept by general practitioners. The coordinating centre will seek agreement — in the name of the local medical collaborator — from patients' general practitioners to invite these patients to the local study clinic. The coordinating centre will then invite — again, in the name of the local medical collaborator — potentially eligible patients to attend specific Screening appointments in the local SEARCH clinic. Patients will be asked to confirm their attendance or, if they wish, to change their appointment by telephoning the Oxford coordinating centre on a 24-hour Freefone number. An updated schedule of clinic appointments will be sent regularly from the coordinating centre to each collaborating clinic.

3.2 SCREENING CLINIC VISIT (-2 MONTHS)

Relevant medical history and eligibility recorded

For all patients attending the Screening visit, the relevant past medical history and other factors relevant to eligibility (including any current use of a statin) are to be recorded by the clinic nurse directly onto the Screening Form. The clinic nurses are to check the study inclusion and exclusion criteria, and to record height, weight and blood pressure. All Screened patients are to be given dietary advice similar to that contained in the American Heart Association stage 1 diet guidelines and other personalised information about modification of risk factors for vascular disease. Any noteworthy conditions identified at Screening that might require further investigation or treatment may be brought to the attention of the patient's own doctors by the clinic staff.

Invitation to participate in the randomised study and patient consent sought

Those patients who appear to be eligible for the randomised trial are to be given the Information Leaflet (Appendix 1) and to have the study explained to them by the clinic nurse. Patients should have an opportunity to initiate any discussion they wish during the initial Screening visit, and have time to think about the invitation to participate in the study — perhaps discussing it first with their family or general practitioner — before making a final decision. (Eligible patients who wish to do this will be asked to attend a Consent Pending visit about one week later.) All patients who agree to participate are to be asked for their written consent in a form acceptable to the research ethics committee (Appendix 2). Patients are to be **discouraged** from participating if it is thought unlikely that they would be willing and able to continue attending the Follow-up clinics for at least 5 years.

Blood sample taken and pre-randomisation Run-in treatment provided

A non-fasting blood sample is to be taken at the initial Screening visit (or, for those who defer their decision, at a subsequent Consent Pending visit) from all patients who agree to participate in the study. Those patients are then to be given a Run-in treatment pack containing a 10-week calendar-strip supply of 20 mg simvastatin and placebo-vitamin tablets, and instructed to stop taking any current **non-study** statin therapy. An appointment for the patient to attend a Randomisation visit will then be arranged for about two months later. Patients are to be told to telephone the 24-hour service at any time during the study to change their appointment if it is inconvenient, or to make an earlier appointment if they are having any problems. (Those on oral anticoagulants will be advised to have their anticoagulant dose checked by their general practitioner or local anticoagulant clinic in about one week.)

At the end of each clinic day, all blood samples (along with top copies of all completed visit forms) are to be sent by courier to the coordinating centre for immediate laboratory assay. The general practitioner of each patient started on Run-in treatment will be informed by the coordinating centre of their patient's current lipid lowering medication and blood lipid profile and biochemistry. (For patients on oral anticoagulants, the general practitioner will also be advised to check prothrombin times about one week after Run-in therapy begins.) This allows the patient's own doctor to decide, during the 2-month Run-in period prior to randomisation, whether they wish that patient to be randomised. Patients in whom significantly elevated blood liver enzymes, creatinine or CK are identified by the central laboratory will be advised by the coordinating centre to stop taking the Run-in treatment and to return any that remains.

3.3 RANDOMISATION CLINIC VISIT (0 MONTHS)

Final check of eligibility and compliance before randomisation

Patients who attend their Randomisation clinic appointment at the end of the 2-month Run-in period will be asked if they have suffered MI, hospitalisation for angina, coronary revascularisation or any other significant problems during the Run-in period. Details are to be recorded directly onto the Randomisation Form, and compliance with taking Run-in treatment checked (i.e. about 90% or more of the scheduled study treatment should have been taken: all remaining Run-in medication is to be retrieved and returned at regular intervals to the coordinating centre). All non-study treatments taken regularly by the patient are to be recorded. Compliant patients who have not had a major vascular event or other significant problem during the Run-in period, and are not on a contraindicated drug, are to be asked if they are still willing to continue taking study treatment for at least the next 5 years. If they are, a non-fasting blood sample is to be taken for central laboratory assay, and for storage in liquid nitrogen for any subsequent analyses required.

Random allocation of study treatment

The central 24-hour telephone service at the coordinating centre (CTSU, Oxford) is then to be telephoned:

0800-585323 (Freefone) or 01865-240972

This telephone call allows the coordinating centre to perform a final check of eligibility prior to randomisation, to obtain any missing baseline data, and to stratify the

randomisation with respect to important patient characteristics. After a few brief details have been provided, a Randomisation treatment pack number will be specified and this is to be recorded on the Randomisation Form. An appointment will also be allocated for the first post-randomisation Follow-up clinic visit in about 2 months, and this is to be confirmed or, if not convenient for the patient, changed.

After the telephone call is completed, the patient is to be given the correct numbered Randomisation treatment pack. This contains a 20-week calendar-strip supply of simvastatin (80 mg active tablet plus 20 mg placebo tablet, or 20 mg active tablet plus 80 mg placebo tablet daily) and of supplement (2 mg folic acid plus 1 mg vitamin B₁₂ daily, or matching placebo). The patient's general practitioner will be informed of their patient's randomisation and provided with the full blood lipid profile from this visit (i.e. while the patient was taking 20 mg daily simvastatin) and haematology results. If vitamin B₁₂ levels are below the 5th percentile then the patient will be referred to their own doctor for any investigations and management (e.g. intramuscular injection of vitamin B₁₂) considered appropriate, but study treatment should generally continue unchanged. (For patients on oral anticoagulants, the general practitioner will also be advised to check prothrombin times about one week after randomisation.)

3.4 POST-RANDOMISATION FOLLOW-UP (2, 4, 8 & 12 MONTHS, THEN 6-MONTHLY)

Recording adverse events and compliance

After randomisation, patients are to be seen in the clinic for routine Follow-up checks for cardiovascular events and any other serious adverse events, first at 2, 4, 8 and 12 months post-randomisation, and then at 6-monthly intervals. Details are to be recorded directly onto the Follow-up Form of the main reason(s) for all hospital admissions (including day cases) and of any suspected myocardial infarction, coronary or other revascularisation procedures, stroke, venous thromboembolism, cancer, or other serious adverse experiences. Patients are also to be asked if they have had significant new and unexplained muscle pain or weakness, or any other adverse experience. Any adverse experience, whether serious or not, that is considered to be probably due to study treatment will be recorded on the Follow-up Form. (See Section 3.6 for additional requirements for reporting **serious** adverse experiences believed to be **due to study treatment**.) Use of regular non-study treatment and compliance with the study treatment is to be checked and, for patients who stop study treatment, the reason(s) for doing so recorded. (N.B. Only when study treatment has been stopped permanently is any remaining study treatment to be retrieved from the patient and returned to the coordinating centre.)

Blood sample taken and study treatment provided

At each routine Follow-up visit, a non-fasting blood sample is to be taken for immediate central laboratory assay of ALT and CK. Full blood counts will be measured at the 1-year and 4-year Follow-up visits. (Each year, from a small random sample of patients, an extra blood sample will also be collected and analysed in detail, and stored in liquid nitrogen for subsequent analyses: see Section 3.7.)

The patient is then to be given a further supply of their study treatment (except at the first 2-month Follow-up visit), and encouraged to keep taking it every evening for the duration of the study. Follow-up treatment packs provided at the 4-month and 8-month Follow-up visits contain a 20-week calendar-strip supply, and subsequent packs contain a 26-week supply. (Consequently, patients should have a surplus of 8 weeks' supply by month 12, which is maintained throughout the remainder of the study. This should help ensure that patients do not run out of study treatment if any slight extension occurs in the interval between Follow-up visits.)

An appointment should then be arranged for the patient's next scheduled clinic visit. Clinic staff in any doubt about an individual patient's management are to discuss it either with their local medical collaborator or with one of the clinical coordinators in the Oxford coordinating centre.

Telephone Follow-up for randomised patients not attending Clinic Follow-up

All randomised patients, irrespective of whether or not they continue to take study treatment, are to be encouraged to attend their routine Follow-up clinic visits. If, however, a randomised patient becomes definitely unwilling or unable to attend the Follow-up clinics, then the clinic nurse is to telephone the patient at the time of each of the scheduled Follow-up visits in order to complete the Follow-up Form. Patients who stop attending clinic follow-up will be asked to return their regular study treatment — but, if appropriate, they can then be provided with supplement-only (i.e. folic acid plus vitamin B₁₂, or matching placebo) packs by mail. In such cases, the clinic nurse should complete a Treatment Pack Request Form and send it to the coordinating centre.

3.5 EARLY RECALL CLINIC VISITS AND MODIFYING STUDY TREATMENT

Monitoring significant biochemical abnormalities or other problems

Following randomisation, biochemical abnormalities requiring action will be reported back to the clinic staff promptly by the coordinating centre, and appropriate arrangements to attend an Early Recall visit will be made with the patient by the coordinating centre. Early Recall visits may also be arranged if the patient wishes to be seen before their scheduled Follow-up visit, or if the clinic nurse believes this would be useful. The planned monitoring procedures for significant biochemical abnormalities are summarised below (see Hospital Manual for details):

ALT: Elevation of ALT >4xULN is to result in an Early Recall visit within about 1 week, while ALT >2xULN but ≤4 xULN is to be checked within about 3 weeks. If repeat ALT >4xULN then study simvastatin treatment should be stopped temporarily; whereas if >2 but ≤4xULN, ALT is to be checked again in about 3 weeks, with study simvastatin treatment then stopped temporarily if ALT remains >2xULN. After stopping study simvastatin treatment temporarily, ALT is to be checked again in about 6 weeks and study simvastatin treatment stopped permanently if still >1.5xULN (with 3-weekly Early Recall visits until ALT reverts to normal: i.e. ≤1.5xULN). If, on the other hand, ALT ≤1.5xULN then the allocated study simvastatin treatment can be started again after review by one of the study medical coordinators, with a further 3 Early Recall visits at 4-week intervals (at which ALT must remain ≤2xULN, otherwise study simvastatin treatment is to be stopped permanently).

CK: Elevation of CK >10xULN with unexplained muscle symptoms is to result in the study simvastatin treatment being stopped immediately and permanently, and an Early Recall visit arranged within about 1 week (with 3-weekly Early Recall visits until CK reverts to normal: i.e. ≤3xULN). Any other CK >5xULN is to result in an Early Recall visit within about 1 week for repeat sample, and if repeat CK >5xULN then study simvastatin treatment should be stopped temporarily. CK is to be checked again in about 6 weeks and study simvastatin treatment stopped permanently if still >3xULN. If, on the other hand, CK ≤3xULN then the allocated study simvastatin treatment can be started again after review by one of the study medical coordinators, with a further 2 Early Recall visits at 4-weekly intervals (at which CK must remain ≤3xULN, otherwise study simvastatin treatment is to be stopped permanently).

Modifying study treatment

In addition to biochemical abnormalities (as described above), the following events may be considered sufficient reason to discontinue the simvastatin component of the study treatment:

- **serious** adverse experience **thought likely to be due to study treatment** (see Section 3.6);
- conditions or procedures requiring the use of agents (such as non-study statins, fibrates, high-dose niacin, cyclosporin or nefazodone) that may be contraindicated in patients who may already be receiving high doses of a statin. (N.B. Patients starting treatment with other cholesterol-lowering drugs or diets should remain on the study simvastatin treatment, unless this is thought to be clearly contraindicated.); or
- pregnancy or any other situation where, in the opinion of the patient's own doctors or the clinic staff, continuing the study simvastatin would not be in the patient's best interest.

Patients may also stop the study treatment at their own request, or at the request of their own doctors. But, any patient who stops the study simvastatin would be encouraged to continue attending their routine Follow-up clinic visits and, if appropriate, to continue taking the supplement tablets (i.e. folic acid plus vitamin B₁₂, or placebo). The coordinating centre will inform the patient's general practitioner when study simvastatin is stopped permanently so that they can decide whether or not to start non-study statin therapy.

3.6 REPORTING SERIOUS ADVERSE EXPERIENCES

Immediate reporting of any serious adverse experiences believed to be due to study treatment

To fulfil regulatory authority requirements, **serious** adverse experiences believed with a reasonable probability to be **due to** study treatment should be reported immediately by telephoning the 24-hour service, where a few brief details will be recorded. For the purposes of this study, the only adverse experiences that need to be reported in this way are those that are **both**:

- (i) **serious** (defined as those which result in death or are life-threatening, produce a permanent or substantial disability, result in in-patient hospitalisation or the prolongation of such hospitalisation, or are cancer, congenital abnormality, or the result of an overdose), **and**
- (ii) **believed with a reasonable probability to be due to study treatment.**

Reporting of other serious adverse experiences at routine follow-up

Serious adverse events that are **not** thought to be due to study treatment should **not** be reported in this way. Such events are, however, to be routinely recorded at the Follow-up and Early Recall visits (see Sections 3.4 & 3.5) for central analysis and regular review by the Data Monitoring Committee (see Section 2.5).

3.7 CENTRAL ASCERTAINMENT OF BIOCHEMICAL EFFECTS, AND OF VASCULAR EVENTS, CANCERS AND CAUSE-SPECIFIC MORTALITY

Assessing biochemical efficacy of treatments in a random sample of patients

To assess the overall effects of the study treatments on the levels of plasma lipids, folate, vitamin B₁₂ and homocysteine in this randomised blinded study, it suffices to assay these factors in blood taken from random samples of the patients at intervals during the study. So, about 5-10% of the randomised patients (irrespective of whether or not they continue to

take study treatment or attend study clinics) will be selected randomly by the coordinating centre each year for their blood samples to be analysed extensively and stored in liquid nitrogen.

Confirmation of non-fatal events by the coordinating centre

The coordinating centre will seek confirmation and additional information (including, if necessary, any relevant hospital discharge records) from the patient's general practitioner (and other appropriate sources) about each suspected myocardial infarction, revascularisation procedure, stroke, thromboembolism and cancer (and any other relevant hospitalisations or serious adverse experiences) recorded at the Follow-up or Early Recall visits. In response to results emerging from this and other relevant studies, during and after the scheduled follow-up period, further details may also be sought for other events.

All available information about each relevant event will be reviewed blind to treatment allocation by a clinician not involved in the routine conduct of the study, and the event coded using an adaptation of the READ code system. The diagnosis of MI requires information about either (i) the presence of two or more of: (a) typical ischaemic chest pain, pulmonary oedema, syncope or shock; (b) development of pathological Q-waves and/or appearance or disappearance of localised ST-elevation followed by T-wave inversion in two or more of twelve standard electrocardiograph leads; and (c) increase in concentration of serum enzymes consistent with MI (CK>2xULN); or (ii) necropsy findings of MI of an age corresponding to time of onset of symptoms⁶⁰. ("Silent" MIs are not to be included.) For any strokes reported, information will be sought for review particularly of likely aetiology (i.e. haemorrhagic or not) and severity; and for cancers, information on the primary site will be sought (which may be supplemented by central registry data: see below).

Follow-up of deaths and of non-fatal cancers

The coordinating centre will seek, for all randomised patients, the certified causes of any deaths and details of any registered non-fatal cancers from United Kingdom central registries. Notification of deaths and cancers by these registries is independent of whether patients are still complying with study medication, and of whether they are still attending the clinic for regular follow-up (as long as they remain within the United Kingdom). Consequently, it ensures unbiased cause-specific mortality and site-specific cancer incidence data for all patients.

For each death reported, whether by central registries or other sources, information will be sought from the patient's general practitioner (and other appropriate sources) about the circumstances and likely cause of death. Where appropriate, post mortem and/or coroner's reports will also be sought. All available information about each reported death will be reviewed blind to treatment allocation by a clinician not involved in the routine conduct of the study, and the underlying cause of death coded according to the Ninth International Classification of Diseases (ICD-9).

Independent check of central coding

As an independent check of the central coding of non-fatal events and deaths, the Steering Committee co-chairmen will review a random sample of coded non-fatal events and of deaths blind to the central coding. Disagreements between the central coding and the initial check coding will be resolved by discussion, and this will guide subsequent coding and the extent of further check coding.

You are being invited to join a nationwide study of long-term treatment to prevent further heart attacks and the need for heart surgery. Big differences are not likely, so the study is designed to look for small — but worthwhile — differences (and to look for any serious side-effects of long-term treatment). In order not to overlook such effects, about 12,000 men and women in Britain who — like you — have had a heart attack are being invited to participate.

This invitation is made with the agreement of your own doctors. You are, of course, free to choose not to join the study (or, if you do decide to take part, to withdraw from the study treatment at any time) without affecting the medical care you can expect from your own doctors. If, after reading this leaflet, you have any questions, then please discuss them either with the study clinic staff or with your own doctor.

Cholesterol and heart disease

Heart attacks (“coronaries”) are the leading cause of death in Britain. One of the main things that makes a heart attack more likely is having too much cholesterol (a fatty substance) in the blood. Some cholesterol in the bloodstream is necessary for normal body processes, but too much of it can narrow the vessels supplying blood to the heart and so increase the chances of having a heart attack. Blood cholesterol levels may be too high in most British men and women. Cholesterol levels in the blood can be reduced by reducing the amount of animal fat in the diet, and you will have been given information about how to do this (for example, by eating less butter, cheese and fatty meat). In addition, blood cholesterol levels can be further reduced by special cholesterol-lowering drugs, such as the “statins” (trade names: Lescol, Lipitor, Lipobay, Lipostat, Zocor).

Millions of people worldwide are taking these drugs, and they have been widely studied — particularly in patients who have already had heart attacks. Lowering cholesterol has been shown clearly to reduce the chances of having another heart attack or of needing heart surgery, and it seems that bigger cholesterol reductions may produce bigger benefits. But, more intensive lowering of cholesterol might have some unsuspected adverse effects that counterbalance any further reduction in heart attacks. The purpose of this study, “SEARCH”, is to find out whether lowering cholesterol to a greater extent with a higher dose of the statin called simvastatin (trade name: Zocor), rather than with a standard dose, produces worthwhile benefits.

Vitamins and heart disease

Although your level of cholesterol affects your chances of having a heart attack, other factors (particularly cigarette smoking and high blood pressure) also play a part. There have been suggestions that certain vitamins (in particular, folic acid and vitamin B₁₂) can help protect against heart attacks, but this is unproven. Moreover, taking regular supplements of these vitamins may have little or no beneficial effect among people living in a country, such as Britain, where most may get adequate amounts in their diet. It is also possible that long-term use of some of these vitamins could, on balance, be slightly harmful, but this too is unproven. It is not yet known whether these vitamins are of any importance in reducing the chances of having a heart attack or in saving lives. SEARCH will help to answer this question.

What taking part in SEARCH involves

SEARCH will involve many thousands of men and women from around Britain. Like you, they are being invited to take part because they have had a heart attack and statin treatment is considered to be necessary. Everyone taking part will have agreed to do so voluntarily, knowing that it may involve them in taking study treatment for 4-5 years.

The cholesterol-lowering comparison in the study involves taking 2 tablets each day. The small tan tablet contains either a standard dose of simvastatin (20 mg) or a similar-looking inactive substance (called a "placebo"), and the red capsule-shaped tablet contains either a larger dose of simvastatin (80 mg) or a matching placebo. For each patient, only one of these two tablets will really contain simvastatin — that is, by taking both tablets each day you would receive either 20 mg or 80 mg simvastatin. In addition, for the vitamin-supplement comparison, a white tablet is to be taken daily, containing either 2 mg of folic acid plus 1 mg of vitamin B₁₂, or a similar-looking placebo. All of your other medical care will be left unchanged, except that you would be asked to stop any other statin tablets prescribed by your own doctor.

The type of study treatment being taken — whether standard-dose or higher-dose simvastatin, and whether active or dummy vitamin supplement — will not generally be known by you, or by the research clinic nurse, or by your doctor. This information will be known only by the staff at the central administration, but it would be made available to your own doctor if this was ever medically necessary. This design ensures that reliable information will be obtained about the effects of these potentially important treatments.

If you decide to join the study

If you do choose to participate in SEARCH, you will be given a box of conveniently packaged study treatments and asked to take one 20mg simvastatin tablet and one supplement tablet every evening for the next 2 months. After completing these first 2 months, you will be seen again in the clinic, and can decide whether or not you would be willing to take study treatment long-term. If so, you would be given supplies of the study treatment (3 tablets each evening, as described above) and would be seen after 2, 4, 8 and 12 months in the first year, and then every 6 months for about 4 more years. In general, these visits to the study clinic should involve very little waiting and should take no more than about 15 minutes.

Side-effects with standard doses of simvastatin are extremely uncommon, and usually are not serious and disappear on stopping treatment. Experience with higher doses is more limited, so you will be monitored carefully by the clinic nurses throughout the study. In a small proportion of patients taking simvastatin or other statins, changes in blood measurements related to the liver (which have only very rarely been associated with any liver problems) or muscles (which are occasionally associated with muscle pain or weakness) have been observed. Such problems may be more common, particularly with higher doses of statins, in patients who are also taking certain other cholesterol-lowering drugs (that is, "fibrates" or high-dose niacin), cyclosporin, an antidepressant called Dutonin, methotrexate, certain "azole" antifungal drugs and the "macrolide" antibiotics clarithromycin and erythromycin. Consequently, patients who have serious liver or muscle disease, or who are taking these other drugs, should not enter the study — and nor should women who are likely to become pregnant. As a safety check in the study, a small blood sample will be collected each time we see you so that liver and muscle measurements can be made (but cholesterol will not be re-measured routinely). Some blood samples will also be stored for future analyses.

The doses of folic acid and vitamin B₁₂ being used in this study are somewhat higher than are commonly taken. Such doses are not known to cause any particular problems, but again we shall monitor their effects carefully. If you do join the study then you would be asked to avoid taking non-study folic acid supplements (but would be free to take other vitamin supplements).

If, after joining the study, you do develop some unexpected symptoms — in particular, soreness or weakness of your muscles which is not the result of exercise or some other activity — you should contact one of the staff in the study clinic, or in the coordinating centre on the 24-hour Freefone service: 0800-585323. (N.B. If you are taking an oral anticoagulant, like warfarin, then the dose will need to be checked by your doctor when the study tablets are started, and when they are stopped for more than a few days.)

Long-term collaboration

Participation in this study will require a commitment to take the study treatment for at least 4 years, with regular visits to the clinic. **If you do not think that you would be willing or able to do this then it would be better not to join in the first place.** (Unfortunately, we are not able to reimburse travel expenses routinely.) If you do decide to take part, you would, of course, be free to withdraw from the study treatment at any time without necessarily giving any reason (and without adversely affecting the medical care you can expect from your own doctors). In particular, you will be encouraged to withdraw after the first 2 months if you have any second thoughts or problems with study treatment or clinic attendance. If you do stop during the first 2 months then no further enquiries will be made of you. But, if you decide to continue, then we would like to see you regularly for the next 4-5 years to check on your health — even if you stop taking the study treatment during this period. **Throughout the study, your own doctors would remain fully responsible for all your other medical care, as usual.**

The important details of your progress will be sent to the study coordinating centre in Oxford. The coordinating centre will seek information from participating patients' own doctors and from central registries about any serious illnesses (such as heart attacks, strokes, cancers, etc) that occur. All such information will be used, **in confidence**, only for medical research purposes and for routine regulatory and audit purposes.

**If you have any questions about the study
then please feel free to ask the clinic staff**

N.B. SEARCH involves the collaboration of several dozen British hospitals, and is organised centrally by the British Heart Foundation supported Clinical Trial Service Unit at the University of Oxford. The study is funded by the manufacturers of simvastatin (Merck Sharp & Dohme), but it is conducted independently of the pharmaceutical company.

Thank you for your help



Agreement to participate

You have already been given the Information Leaflet about the SEARCH medical research project. If you want any further information before deciding whether to join the study, then please ask now. (Alternatively, if you want to delay your decision for a time, perhaps to discuss matters further with your own doctor, then please make an appointment to come back later.)

If you do now decide to join the study and then sometime later find there is some aspect of it that you wish to discuss further, then please feel free to contact me or another of the study clinic's staff.

Signature of study staff:

PRINTED name:

Date: / / Telephone:

If a lot of people do choose to join this study and stay in it, then reliable results will eventually emerge that will help the thousands of people who have been in the study and the millions who have not. But, if you would prefer not to join, or think that you might well not want to stay in the study for 4-5 years, then please feel free to refuse this invitation.

If you do choose to join the study now, there will be a second occasion (in about 2 months) when you will be asked to consider whether you wish to continue. If you do stop during this first two months, then no further enquiries will be made of you. But, if you decide to continue, then we would like to see you regularly for about the next 4-5 years to check on your health — even if you stop taking the study treatment during this period. Throughout the study, your own doctors would remain fully responsible for all your other medical care, as usual.

Signature by patient:

I have been informed about SEARCH and agree to enter it. I hope to collaborate in this study for several years, but understand that I am free to withdraw from the study treatment at any time without necessarily giving any reason (and without adversely affecting the medical care I can expect from my own doctors). I agree that samples of my blood may be stored for any future analyses required, and that information about any serious illnesses (such as heart attacks, strokes, cancers, etc.) may be supplied to the study coordinators by my own doctors and by central registries. This is on the understanding that such information would remain confidential and be used for medical research only.

Patient's signature:

PRINTED name:

Date: / / Telephone:

**The top copy is to be returned to the coordinating centre,
the middle copy retained by clinic staff,
and the bottom copy given to the patient.**

REFERENCES

- 1 Martin MJ, Hulley SB, Browner WS, Kuller LH, Wentworth D. Serum cholesterol, blood pressure and mortality: implications from a cohort of 361,662 men. *Lancet* 1986; ii: 933-936
- 2 Stamler J, Vaccaro O, Neaton JD, Wentworth D for the Multiple Risk Factor Intervention Trial Research Group. Diabetes, other risk factors and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993; 16: 434-444
- 3 Keys A. *Seven Countries: A multivariate analysis of health and coronary heart disease.* Harvard University Press, 1980
- 4 Jacobs D, Blackburn H, Higgins M et al. Report of the conference on low blood cholesterol: mortality associations. *Circulation* 1992; 86: 1046-1060
- 5 Chen J, Campbell TC, Li J, Peto R. *Diet, Life-style and Mortality in China.* Oxford University Press 1990
- 6 Chen ZM, Peto R, Collins R et al. Serum cholesterol concentration and coronary heart disease in population with low cholesterol concentrations. *BMJ* 1991; 303: 276-282
- 7 Szatrowski TP, Peterson AV, Shimizu Y et al. Serum cholesterol levels, other risk factors, and cardiovascular disease in a Japanese cohort. *J Chron Dis* 1984; 7: 569-584
- 8 Peto R, Yusuf S, Collins R. Cholesterol lowering trials in their epidemiological context. *Circulation* 1985; 72: 451 (abstract)
- 9 Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? *BMJ* 1994; 308: 367-373
- 10 Gould AL, Rossouw JE, Santanello NC, Heyse JF, Furberg CD. Cholesterol reduction yields clinical benefit. A new look at old data. *Circulation* 1995; 91: 2274-2282
- 11 Grundy SM. HMG-CoA reductase inhibitors for treatment of hypercholesterolemia. *New Engl J Med* 1988; 319: 24-33
- 12 Jones P, Kafonek S, Laurora I, Hunninghake D for the CURVES Investigators. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin and fluvastatin in patients with hypercholesterolemia (the CURVES study). *Am J Cardiol* 1998; 81: 582-587
- 13 Keech A, Collins R, MacMahon S, Armitage J, Lawson A et al for the Oxford Cholesterol Study Group. Three-year follow-up of the Oxford Cholesterol Study: assessment of the efficacy and safety of simvastatin in preparation for a large mortality study. *Eur Heart J* 1994; 15: 255-269
- 14 Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Study (4S). *Lancet* 1994; 344: 1383-1389
- 15 Scandinavian Simvastatin Survival Study Group. Baseline serum cholesterol and treatment effect in the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1995; 345: 1274-1275
- 16 Sacks FM, Pfeffer MA, Moye LA et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996; 335: 1001-1009
- 17 Shepherd J, Cobbe SM, Ford I et al for the West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolaemia. *N Engl J Med* 1995; 333: 1301-1307
- 18 Collins R, Keech A, Peto R et al. Cholesterol and total mortality: need for larger trials. *BMJ* 1992; 304: 1689 (letter)
- 19 Cholesterol Treatment Trialists' (CTT) Collaboration. Protocol for a prospective collaborative overview of all current and planned randomized trials of cholesterol treatment regimens. *Am J Cardiol* 1995; 75: 1130-1134
- 20 Oliver MF. Statins prevent coronary heart disease. *Lancet* 1995; 346: 1378-1379
- 21 Davey Smith G, Pekkanen J. Should there be a moratorium on the use of cholesterol lowering drugs? *BMJ* 1992; 304: 431-434
- 22 Newman TH, Hulley SB. Carcinogenicity of lipid-lowering drugs. *JAMA* 1996; 275: 55-60
- 23 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering drug therapy and of antioxidant vitamin supplementation in patients at increased risk of coronary heart disease: design, study population and early experience. *Eur Heart J* (submitted)
- 24 Davidson MH, Stein EA, Dujovne CA et al. The efficacy and six-week tolerability of simvastatin 80 and 160 mg/day. *Am J Card* 1997; 79: 38-42
- 25 Pedersen TR, Tobert JA. Benefits and risks of HMG-CoA reductase inhibitors in the prevention of coronary heart disease; a reappraisal. *Drug Safety* 1996; 14: 11-24
- 26 Nawrocki JW, Weiss SR, Davidson MH et al. Reduction of LDL cholesterol by 25% to 60% in patients with primary hypercholesterolemia by atorvastatin, a new HMG CoA reductase inhibitor. *Art Thromb Vasc Biol* 1995; 15: 678-682
- 27 McCully KS. Vascular pathology of homocysteinemia: implications for the pathogenesis of arteriosclerosis. *Am J Pathol* 1969; 56: 111-128
- 28 Mudd SH, Levy HL, Skovby F. Disorders of trans-sulfuration. In: Scriver CP, Beaudet AL, Sly WS et al, eds. *The Metabolic Basis of Inherited Disease.* New York: McGraw-Hill Book Co; 1989: 693-734
- 29 Selhub J, Miller JW. The pathogenesis of homocysteinemia: interruption of the coordinated regulation by S-adenosylmethionine of the remethylation and transsulfuration of homocysteine. *Am J Clin Nutr* 1991; 55: 131-138
- 30 McCully KS, Wilson RB. Homocysteine theory of arteriosclerosis. *Atherosclerosis* 1975; 22: 215-227

- 31 Wilcken DEL, Wilcken B. The pathogenesis of coronary artery disease: a possible role for methionine metabolism. *J Clin Invest* 1976; 57: 1079-1082
- 32 Ueland PM, Refsum H. Plasma homocysteine, a risk factor for vascular disease: plasma levels in health, disease and drug therapy. *J Lab Clin Med* 1989; 114: 473-501
- 33 Jacques PL, Bostom AG, Williams RR et al. Relation between folate status, a common mutation in methylenetetrahydrofolate reductase, and plasma homocysteine concentrations. *Circulation* 1996; 93: 7-9
- 34 Boushey CJ, Beresford SAA, Omenn GS, Motulsky AG. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. Probable benefits of increasing folic acid intakes. *JAMA* 1995; 274: 1049-1057
- 35 Mayer EL, Jacobson DW, Robinson K. Homocysteine and coronary atherosclerosis. *JACC* 1996; 27: 517-527
- 36 Clarke R, Daly L, Robinson K et al. Hyperhomocysteinemia: an independent risk factor for vascular disease. *N Engl J Med* 1991; 324: 1149-1155
- 37 Malinow MR, Nieto FJ, Szklo M, Chambless LE, Bond G. Carotid artery intimal-medial wall thickening and plasma homocyst(e)ine in asymptomatic adults: the Atherosclerosis Risk in Communities Study. *Circulation* 1993; 87: 1107-1113
- 38 Selhub J, Jacques PF, Bostom AG et al. Association between plasma homocysteine concentrations and extracranial carotid-artery stenosis. *N Engl J Med* 1995; 332: 286-291
- 39 Arnesen E, Refsum H, Bønaa KH, Ueland PM, Førde OH, Nordrehaug JE. Serum total homocysteine and coronary heart disease. *Int J Epidemiol* 1995; 25: 704-709
- 40 Perry I, Refsum H, Morris RW et al. Prospective study of serum total homocysteine concentration and risk of stroke in middle aged British men. *Lancet* 1995; 346: 1395-1398
- 41 Graham IM, Daly LE, Refsum HM et al. Plasma homocysteine as a risk factor for vascular disease: the European Concerted Action Project. *JAMA* 1997; 277: 1775-1781
- 42 Nygard D, Nordrehaug JE, Refsum H et al. Plasma homocysteine levels and mortality in patients with coronary artery disease. *N Engl J Med* 1997; 337: 230-236
- 43 Wall RT, Harlan JM, Harker LA, Striker GE. Homocysteine-induced endothelial cell injury in vitro. *Throm Res* 1980; 18: 113-121
- 44 Tsai J, Perrella MA, Yoshizumi M et al. Promotion of vascular smooth muscle cell growth by homocysteine: a link to atherosclerosis. *Proc Natl Acad Sci USA* 1994; 91: 6369-6373
- 45 Heinecke JW, Rosen H, Suzuki LA, Chait A. The role of sulfur-containing amino acids in superoxide production and modification of low density lipoprotein by arterial smooth muscle cells. *J Biol Chem* 1987; 262: 98-103
- 46 Lentz SR, Sadler JE. Inhibition of thrombomodulin surface expression and protein C activation by the thrombogenic agent homocysteine. *J Clin Invest* 1991; 88: 1906-1914
- 47 Nygard O, Vollset SE, Refsum H et al. Total plasma homocysteine and cardiovascular risk profiles. The Hordaland Homocysteine Study. *JAMA* 1995; 274: 1526-1533
- 48 Ubbink JB, Vermaak WJH, Van der Merwe A, Becker PJ. Vitamin B₁₂, vitamin B₆, and folate nutritional status in men with hyperhomocysteinemia. *Am J Clin Nutr* 1993; 57: 47-53
- 49 Selhub J, Jacques PF, Wilson PWF, Rush D, Rosenberg IH. Vitamin status and intake as primary determinants of homocysteinemia in an elderly population. *JAMA* 1993; 270: 2693-2698
- 50 Subar AF, Block G, James LD. Folate intake and food sources in the US population. *Am J Clin Nutr* 1989; 50: 508-516
- 51 Expert Advisory Group. Folic acid and the prevention of neural tube defects. Department of Health, London, UK, 1992 (DH003594)
- 52 Gregory J, Foster K, Tyler H, Wiseman M. The dietary and nutritional survey of British adults. HMSO, London 1990
- 53 Homocysteine Lowering Trialists' Collaboration. Lowering blood homocysteine with folic acid based supplements: meta-analysis of randomised trials. *BMJ* 1998; 316: 894-898
- 54 Stampfer MJ, Malinow MR. Can lowering homocysteine levels reduce cardiovascular risk? *N Engl J Med* 1995; 332: 328-329
- 55 Lindenbaum J, Healton EB, Savage DG et al. Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. *N Engl J Med* 1988; 318: 1720-1728
- 56 Stabler SP, Allen RH, Savage DG, Lindenbaum J. Clinical spectrum and diagnosis of cobalamin deficiency. *Blood* 1990; 76: 871-881
- 57 Savage DG, Lindenbaum J. Folate-cobalamin interactions. In: *Folate in Health and Disease*. Ed L B Bailey. Marcel Dekker Inc 1995
- 58 Campbell NRC. How safe are folic acid supplements? *Arch Intern Med* 1996; 156: 1638-1644
- 59 Peto R, Pike MC, Armitage P et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Part I: Introduction and design. *Br J Cancer* 1976; 34: 585-612. Part II: Analysis and examples. *Br J Cancer* 1977; 35: 1-39
- 60 World Health Organization. Ischaemic heart disease registers: report of the Fifth Working Group, including a second revision of the operating protocol (April 26-29, 1971). Copenhagen; WHO Regional Office for Europe, 1971

**STEERING AND DATA MONITORING COMMITTEES,
AND CONTACT DETAILS FOR COORDINATING CENTRE**

**STEERING COMMITTEE
(Major organisational and policy decisions)**

Co-chairmen: P Sleight, T Meade
Study coordinators: R Collins, J Armitage
Laboratory director: L Youngman
Statistician: S Parish
Administrative coordinators: J Barton, C Bray
Other members: R Clarke, I Graham, D Simpson, C Warlow
Observer: J Tobert (Merck Sharp & Dohme)

**DATA MONITORING COMMITTEE
(Interim analyses and response to specific concerns)**

Chairman: R Doll
Vice-chairman: L Wilhelmsen
Members: K Fox, C Hill, P Sandercock
Statistician to the Data
Monitoring Committee: R Peto (non-voting)

**COORDINATING CENTRE, CLINICAL TRIAL SERVICE UNIT, OXFORD
(Training, monitoring and queries; supply of drugs and other study materials;
arranging clinic appointments; collection and analysis of data and blood)**

Administrative coordinators: Miss Jill Barton, Dr Chris Bray
Clinical coordinator: Dr Jane Armitage
Nurse coordinator & liaison: Ms Jacinta Godden, Mrs Alette Lawson
Laboratory director: Dr Linda Youngman
Computing: Dr Peter Harding, Dr Mike Lay,
Mr Karl Wallendszus

**SEARCH (CTSU)
FREEPOST
Harkness Building
Radcliffe Infirmary
Oxford OX2 6YZ
(No stamps needed in UK)**

Office telephone: 01865-404818
(answering machine outside office hours)
Office telefax: 01865-404821

**24-HOUR TELEPHONE SERVICE: For clinic appointments,
randomisation, urgent queries, unblinding and reporting serious
adverse experiences believed to be due to study treatment:**

0800-585323 (Freefone) or 01865-240972